History of cirrhosis and risk of digestive tract neoplasms

G. Randi1,2*, A. Altieri1, S. Gallus1, S. Franceschi2, E. Negri1, R. Talamini3 & C. La Vecchia1,4

1Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy; 2International Agency for Research on Cancer, Lyon, France; 3Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano (PN), Italy; 4Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy

Received 15 February 2005; revised 7 April 2005; accepted 15 April 2005

Background: Cirrhosis is strongly related to liver cancer. Data on the possible association between cirrhosis and risk at other cancer sites are scanty.

Patients and methods: We analysed data from a network of case–control studies conducted in Italy between 1983 and 1997, including patients with cancers of the oral cavity and pharynx (520), oesophagus (405), stomach (731), rectum (613), liver (425), gallbladder (63) and pancreas (395). The controls were 4297 patients admitted to hospitals for acute non-neoplastic conditions.

Results: After strict allowance for alcohol drinking, tobacco smoking and history of hepatitis, the multivariate odds ratios for a history of cirrhosis were 4.7 [95% confidence interval (CI) 2.2–9.8] for neoplasms of the oral cavity and pharynx, 2.6 (95% CI 1.2–5.7) for the oesophagus, 1.0 (95% CI 0.4–2.5) for the stomach, 1.0 (95% CI 0.4–2.4) for the colon, 1.7 (95% CI 0.7–4.1) for the rectum, 20.5 (95% CI 12.3–34.2) for the liver, 2.1 (95% CI 0.3–16.8) for the gallbladder and 0.9 (95% CI 0.3–3.0) for the pancreas.

Conclusions: Our study confirms and further quantifies the increased risk of liver cancer in cirrhotic patients and is compatible with an increased risk of oral, pharyngeal and oesophageal cancers.

Key words: cancer, cirrhosis, digestive tract, risk

Introduction

Patients with cirrhosis are at increased risk of primary liver cancer [1, 2]. However, cirrhosis could affect cancer risk at other sites [2–4] but limited data are available on the issue.

A population-based cohort study from Denmark including 11 605 patients diagnosed with cirrhosis and a total of 1447 cancers at different sites found a standardized incidence ratio of 2.0 [95% confidence interval (CI) 1.9–2.2] for all cancers and 36.0 (95% CI 31.6–40.8) for primary liver cancer [2]. Excess risk was found for all alcohol- and tobacco-related malignancies, such as lung, laryngeal, oral and pharyngeal, stomach, pancreas, bladder and kidney cancers. Moderate positive associations were reported for colon and breast cancers. However, no adjustment was possible for potential confounders, including alcohol and tobacco consumption.

Some studies have focused on the relation between cirrhosis and the risk of digestive tract cancers. A prospective study among black males discharged from US Veterans Administration Hospitals with a diagnosis of cancer showed that cirrhotic patients had a 2.5-fold excess risk for additional primary upper digestive tract cancer (mouth, pharynx and oesophagus) compared with non-cirrhotic patients, and suggested that the duration of cirrhosis was a significant predictor of risk [5]. An Italian cohort study of 1379 patients with cirrhosis followed for 15 years found a significant 2.6-fold increased risk of gastric cancer compared with the general population [6].

A retrospective study based on 4131 cases of gastric cancer from the USA found a significant excess risk of 1.5 for gastric cancer only among patients with cirrhosis that lasted for >_7 years [7].

In order to explore further the possibility that cirrhosis plays a role in the carcinogenesis of various digestive tract cancers, we analysed data from an integrated network of Italian case–control studies. The availability of a large number of covariates allowed us to control for potential confounding effects.

Materials and methods

Data used in this study were obtained from an integrated series of hospital-based case–control studies conducted in Italy between 1983 and 1997 [8, 9]. The studies included subjects admitted to teaching and general hospitals from the greater Milan area and the province of Pordenone in northeastern Italy.

Cases

Cases were patients aged <80 years with incident (i.e. diagnosed within the year before the interview) and histologically confirmed cancers of
Table 1. Distribution of cases of selected neoplasms and controls and the corresponding odds ratios (ORs) with 95% confidence intervals (CI) according to history and time since diagnosis of cirrhosis (Italy, 1983–1997)

<table>
<thead>
<tr>
<th>Type of neoplasm</th>
<th>No. of subjects</th>
<th>Patients with history of cirrhosis (%)</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>OR&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>520</td>
<td>25 (4.8)</td>
<td>6.8 (3.6–13.0)</td>
<td>4.7 (2.2–9.8)</td>
<td>3.2 (1.9–5.9)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>405</td>
<td>12 (3.0)</td>
<td>3.6 (1.7–7.4)</td>
<td>2.6 (1.2–5.7)</td>
<td>1.9 (0.6–6.4)</td>
</tr>
<tr>
<td>Stomach</td>
<td>731</td>
<td>6 (0.8)</td>
<td>1.1 (0.4–2.7)</td>
<td>1.0 (0.4–2.5)</td>
<td>1.7 (0.6–5.0)</td>
</tr>
<tr>
<td>Colon</td>
<td>943</td>
<td>6 (0.6)</td>
<td>0.9 (0.4–2.3)</td>
<td>1.0 (0.4–2.4)</td>
<td>0.6 (0.1–2.5)</td>
</tr>
<tr>
<td>Rectum</td>
<td>613</td>
<td>7 (1.1)</td>
<td>1.8 (0.8–4.3)</td>
<td>1.7 (0.7–4.1)</td>
<td>3.4 (1.3–9.1)</td>
</tr>
<tr>
<td>Liver</td>
<td>425</td>
<td>84 (19.8)</td>
<td>20.9 (12.7–34.4)</td>
<td>20.5 (12.3–34.2)</td>
<td>23.7 (11.6–48.4)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>63</td>
<td>1 (1.6)</td>
<td>2.2 (0.3–16.8)</td>
<td>2.1 (0.3–16.8)</td>
<td>–</td>
</tr>
<tr>
<td>Pancreas</td>
<td>395</td>
<td>3 (0.8)</td>
<td>0.9 (0.3–2.9)</td>
<td>0.9 (0.3–3.0)</td>
<td>0.7 (0.1–5.6)</td>
</tr>
<tr>
<td>Controls</td>
<td>4297</td>
<td>27 (0.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Reference category is no history of cirrhosis.

<sup>b</sup>Adjusted for sex, age, area of residence, study centre, education and history of hepatitis.

<sup>c</sup>Adjusted for previous variables plus tobacco smoking and alcohol drinking.

the oral cavity and pharynx (444 men, 76 women, median age 56 years), oesophagus (342 men, 63 women, median age 60 years), stomach (452 men, 279 women, median age 61 years), colon (494 men, 449 women, median age 61 years), rectum (367 men, 246 women, median age 62 years), liver (314 men, 111 women, median age 61 years), gallbladder (28 men, 35 women, median age 63 years) and pancreas (256 men, 139 women, median age 60 years).

Controls

Controls were patients aged between 30 and 79 years (median age 56 years) admitted for acute non-neoplastic conditions to the same network of hospitals as the cases. A total of 4297 controls (2912 men and 1385 women) were enrolled. Of these, 36% were admitted for traumatic conditions (mostly fractures and sprains), 20% for non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 28% for acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 16% for other illnesses (such as eye, ear, nose, throat or tooth disorders or dermatological conditions). Specific exclusions were made for any admission related to tobacco smoking and alcohol drinking, including diagnosis of chronic liver conditions, chronic bronchitis, pneumonia, respiratory failure, asthma, cardiovascular disease, peripheral vasculopathies, neurological syndromes and selected nephropathies.

Data collection

All the studies had the same scheme, criteria for subject inclusion and interview setting. Trained interviewers identified and questioned cases and controls and all interviews were conducted during the hospital stay. On average, <5% of eligible cases and controls refused to be interviewed. The questionnaires used for different types of neoplasms included a structured section covering sociodemographic factors, general personal characteristics and habits, and anthropometric measures. Other sections were directed to the investigation of lifestyle habits, including smoking and alcohol consumption in the 2 years before diagnosis, in order to avoid any type of recall bias. The section on alcohol drinking included the number of days per week each alcoholic beverage (i.e. wine, beer and spirits) was consumed, the number of drinks per day and the duration of the habit in terms of number of years. The information on alcohol was reproducible and valid [10, 11]. All questionnaires comprised information on problem-oriented medical history and, in particular, questions on age at medical diagnosis of hepatitis and cirrhosis. The questionnaires did not include a question on type of cirrhosis (alcohol or non-alcohol related), given the difficulties in separating different causes of cirrhosis in a direct interview.

Data analysis

Odds ratios (ORs), as estimators of the relative risk, and the corresponding 95% CIs were derived from unconditional multiple logistic regression, fitted by the method of maximum likelihood [12], including terms for sex, age (quinquennia), study centre, area of residence (northern, central or southern Italy), years of education (<7 years, 7–12 years, ≥13 years), history of hepatitis (yes/no), tobacco smoking (never, ex-smoker, current smoker ≤15, 15–24, ≥25 cigarettes per day) and alcohol drinking (0, 1–8, 9–14, 15–27, 28–41, 42–55, 56–62, >62 drinks per week, plus a continuous term).

Results

Table 1 gives the distribution of cases and controls and the corresponding ORs for various digestive tract neoplasms according to the history of cirrhosis. The prevalence of cirrhosis among cases ranged from 0.6% for colon cancer to 19.8% for liver cancer, while the prevalence among controls was 0.6%. After strict allowance for tobacco smoking and alcohol drinking, we found direct significant associations between history of cirrhosis and the risk of neoplasms of the liver (OR 20.5; 95% CI 12.3–34.2), oral cavity and pharynx (OR 4.7; 95% CI 2.2–9.8) and oesophagus (OR 2.6; 95% CI 1.2–5.7). Non-significant associations were found for rectal (OR 1.7; 95% CI 0.7–4.1) and gallbladder cancer (OR 2.1; 95% CI 0.3–16.8), and no material association was found...
for other digestive tract neoplasms, including stomach, colon and pancreas. Compared with subjects with no diagnosis of cirrhosis, the OR for oral and pharyngeal cancer was 3.2 (95% CI 1.1–9.5) for ≤7 years since diagnosis, and 6.7 (95% CI 2.4–18.8) for >7 years. The corresponding values for oesophageal cancer were 1.9 (95% CI 0.5–6.4) and 2.7 (95% CI 0.9–8.1), respectively. For liver cancer the OR was 23.7 (95% CI 11.6–48.4) for ≤7 years since diagnosis and 16.4 (95% CI 7.8–34.7) for >7 years. No clear pattern of risk for time since diagnosis of cirrhosis was shown for stomach, colon, rectal and pancreatic neoplasms.

Table 2 shows the relation between history of cirrhosis and cancer risk in strata of sex, age, alcohol drinking, tobacco smoking and years of education. We found no appreciable difference in risk across different strata of covariates, although the association with history of cirrhosis was apparently stronger for subjects of younger age for cancers of the oral cavity and pharynx, in the lower level of alcohol drinking for rectal cancer and in the higher level of education for cancers of the oral cavity and pharynx, the rectum and the liver.

Discussion

This study confirms the strong association of cirrhosis with liver cancer [1, 2, 13], with an excess risk of more than 20-fold in patients reporting a history of cirrhosis even after a strict allowance for major identified confounding factors, including alcohol drinking [14, 15], tobacco smoking and clinical history of hepatitis. Hepatitis is in the causal pathway of both cirrhosis and liver cancer, and hence may represent an overadjustment. The OR for liver cancer in the absence of allowance for hepatitis was 30.9 (95% CI 19.0–50.2). The association between cirrhosis and liver cancer was also consistent across strata of major covariates. The risk was stronger in the short period before diagnosis of liver cancer, but was still present for cirrhosis diagnosed >7 years before diagnosis of liver cancer, suggesting that diagnostic ascertainment cannot totally account for the observed association.

In agreement with prospective studies from the USA and Denmark [2, 5], we found an excess risk for oral, pharyngeal and oesophageal cancers. More importantly, we were able to accurately allow for alcohol and tobacco consumption. The increasing risk with passing time since diagnosis of cirrhosis is consistent with the hypothesis of a real association between cirrhosis and these malignancies. After allowance for alcohol, no association was found for gastric cancer. This is only in apparent contrast with the results of three cohort studies from Europe [2, 6] and the USA [7], since no adjustment for alcohol intake was possible in those studies.

An excess risk for cancer of the rectum was found only in patients with a diagnosis of cirrhosis for <7 years. Such an apparent excess risk may be related, at least in part, to a residual effect of high alcohol consumption [2, 16], especially in relation to adenomatous polyps of the colon [17].

We found a higher risk of gallbladder cancer in cirrhotic patients, but estimates were based on a relatively low number
of cases and need to be confirmed by further investigations. Among the other cancers considered, our findings indicate that cirrhosis is not materially associated with cancers of the colon and pancreas.

The excess of risk found for upper digestive tract cancers may still be affected by a residual confounding of tobacco and alcohol consumption. Although the observed difference between ORs before and after adjustment for tobacco and alcohol intake indicates a strong confounding effect of these variables on cancer risk, the risk estimates remained significantly elevated also after further strict allowance for these factors. We had information on recent alcohol drinking only, and it is possible that chronic liver conditions and cirrhosis have modified drinking habits, thus leading to underadjustment of alcohol. Moreover, the translation of this excess risk into population attributable risk is complex, depending on geographic and cultural variations in alcohol and tobacco consumption.

The association observed could be attributed to recall bias, especially for cases of liver cancer that are more sensitised than controls in reporting a history of cirrhosis. However, owing to the severity of the clinical condition of cirrhosis, a systematic misreporting of the disease is unlikely, and the reproducibility of the medical history was satisfactory [18]. Since traumas may be related to alcohol drinking, we repeated the analysis excluding traumatic controls. However, the estimates did not materially change, the ORs for cirrhatics being 4.3 (95% CI 2.0–9.3) for oral and pharyngeal cancer, 2.3 (95% CI 1.0–5.2) for oesophageal cancer, 0.9 (95% CI 0.4–2.4) for stomach cancer, 0.9 (95% CI 0.3–2.3) for colon cancer, 1.7 (95% CI 0.7–4.1) for rectal cancer, 18.9 (95% CI 10.6–33.8) for liver cancer, 2.0 (95% CI 0.2–16.6) for gallbladder cancer and 0.8 (95% CI 0.2–3.0) for pancreatic cancer. The number of subjects with cirrhosis was relatively small for cancer sites other than hepatocellular carcinoma. Thus the risk estimates were unstable and the power inadequate for subgroup analysis.

Cases and controls came from comparable catchment areas, participation was almost complete, the questionnaires were administered under similar conditions and information on alcohol was satisfactorily reproducible and valid [10, 11]. Among other strengths of this study, there is the notably large dataset, with several types of neoplasms of the digestive tract, and the possibility of allowing for a number of potential confounding factors including education, tobacco smoking, alcohol drinking and clinical history of hepatitis.

The carcinogenic effect of cirrhosis may be mediated through two different mechanisms: a direct neoplastic effect of cirrhosis, or a neoplastic effect of alcohol drinking increased by consequences of cirrhosis. In fact, cirrhosis leads to a reduction in the number of functional hepatocytes and a reduced alcohol dehydrogenase activity [16, 19], and hence may contribute to increase the damage caused by ethanol for similar levels of exposure. Furthermore, cirrhosis causes oesophageal varices that can degenerate into variceal bleeding [20], especially in relation to alcohol consumption. Therefore cirrhosis may be responsible for lesions of the upper digestive tract which can favour the carcinogenic process at these sites.

In conclusion, cirrhosis appears to play a role not only in the risk of liver cancer but also in the risk of oral, pharyngeal and oesophageal cancers, which cannot be totally explained by confounding by alcohol drinking or other covariates.

Acknowledgements

The authors thank Dr MG Rumi for her scientific contribution and Mrs I Garimoldi for editorial assistance. This work was supported by the Italian Association for Cancer Research (AIRC/FIRC), the Italian League Against Cancer, the Ministry of Education (COFIN 2003), and the European Research Advisory Board (ERAB).

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